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(54) Title: MUCIN CONTAINING OPHTHALMIC PREPARATIONS

(57) Abstract

The present invention discloses the ophthalmic applications of mucin derived from mammalian milk or milk byproducts. This mucin has been found to be a MUC1 type mucin similar to the transmembrane mucin expressed on the surface of the human eye. The mucin–containing preparations described in this invention can be in the form of an aqueous formulation to be instilled into the eye, or in which the pre–soak or store an object to be inserted into the eye, such as a contact lens, an ointment, or a solid device to be inserted into the conjunctival sac. The preparations disclosed are utilized for the treatment of tear film and ocular surface disorders associated with the signs and symptoms of dry eye. Furthermore, mucin–based formulations are also effective for the relief of symptoms of eye irritation, such as those caused by environmental conditions or by contact lens wear.

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MUCIN CONTAINING OPHTHALMIC PREPARATIONS

FIELD OF THE INVENTION:

The present invention relates to ophthalmic preparations and more specifically relates to ophthalmic preparations for use as a tear film supplement, wherein the preparation comprises a mucin component.

BACKGROUND OF THE INVENTION:

Initial descriptions and models of the tear film described the tear film as including three distinct layers and as being a three-layered, aqueous-dominated tear film. One of the layers comprises a mucin layer which serves primarily to render the hydrophobic ocular surface hydrophilic, so that the aqueous layer comprising the bulk of the tear film will spread evenly over the eye.

Current work in this field has shown that the classic aqueous-dominated tear film model has been replaced by the more probable concept of a mucin-dominated gel. This gel has its highest concentration of mucin at the epithelial surfaces of the cornea and conjunctiva, and the mucin concentration gradually decreases farther out into the tear film. In this model, the presence of mucin remains significant for the structure, stability and function of the entire tear film. Recent studies of the tear film using laser interferometry and confocal microscopy might be including the entire gel layer in indicating that the human tear film is 30 to 40 microns thick, more than four times thicker than earlier estimates.

Based on tear film physiology and clinical observations, tear film abnormalities are commonly designated by focus on a specific deficiency, such as an aqueous tear deficiency, kerato-conjunctivitis sicca (KCS), a mucin deficiency, a lipid abnormality, an impaired lid function, or an epitheliopathy. Although clinically useful, the simplistic concept of a lack of one component of the tear film as the cause of dry eye has given way to a much more sophisticated view of ocular surface disease that involves: (1) the health and regulation of the various glands contributing secretions to the tear film, (2) changes in the tear film itself, such as in osmolality and content of inflammatory mediators, and (3) what is viewed as a sort of "final common

pathway", the subsequent changes to the ocular surface. In fact, many clinicians and authors prefer the term "ocular surface disease" over "dry eye", for it is change to the ocular surface, whatever the original cause, that results in the significant signs and symptoms of dry eye. The discomfort of ocular surface disease is expressed in ocular symptoms, such as dryness, grittiness, burning, soreness or scratchiness, with variation among individuals. These symptoms can also be exacerbated by factors such as environmental conditions and contact lens wear. The combination of varying clinical signs and symptoms has also been termed dry eye syndrome.

Over the past twenty to thirty years many attempts have been made to provide an effective and long lasting treatment of dry eye symptoms, particularly for patients with moderate to severe KCS. These prior art attempts can be categorized on the basis of their physical state: ointments, emulsions, solid devices and aqueous based solutions or gels. Ointments are generally anhydrous preparations based on mixtures of white petrolatum and mineral oil. Because these formulations are greasy and cause blurred vision, they are not widely used other than in cases of severe symptoms, and are mostly limited to application at night just before sleeping. Emulsion based formulations for treating dry eye symptoms have emerged over the past ten years. One approach has been disclosed in a series of U.S. patents: 5,578,586; 5,371,108; 5,294,607; 5,278,151; 4,914,088, all of which are herein incorporated by reference in their entirety. These patents teach the methods and compositions for reducing evaporation of the aqueous layer from the surface of the eye. The method comprises applying an admixture of a charged phospholipid and a non-polar oil over the eye, preferably in the form of a finely divided oil-in-water emulsion. Another approach is described in U.S. patents 4,818,537 and 4,804,539, incorporated herein by reference in their entirety, where liposome compositions in the form of emulsions are claimed to provide enhanced retention on ocular surfaces and therefore thereby alleviate the symptoms of dry eye.

Solid devices, in the form of ocular inserts, have been utilized for longer term symptomatic relief of dry eye. These devices are placed in the eye and slowly dissolve or erode to provide a thickened tear film. Often patients find these devices

attained through the use of carbomer polymers. These carbomer polymers have been found to be bio-adhesive as described in U.S. patents 5,225,196, 5,188,828, 4,983,392 and 4,615,697, all of which are incorporated by reference in their entirety. It is believed that the bio-adhesive properties of the carbomer contributes to longer retention times in the eye. In fact, U.S. patents 5,075,104 and 5,209,927, incorporated by reference in their entirety, teach "that the carbomer polymers appear to function by maintaining or restoring the normal hydration equilibrium of the epithelial cells, protecting the cornea in a manner similar to that believed to be provided by the mucin component of normal tears. Therefore, in theory, the polymers, in addition to being well retained in the eye and providing lubrication, can function as a mucin substitute in the dry eye syndrome where there is a deficiency or absence of the natural mucin component of the normal tears.

Polymers that exhibit mucin-like properties are often referred to as "mucomimetic". Usually in the art the mucin-like property provided by such "mucomimetic" polymers is simply viscosity. While it is true that a viscous solution will stay in the eye somewhat longer, it is the viscoelasticity, rather than simply the viscosity, of the gel-forming mucin of the tear film that is critical to its protective function during blinking. Additional lubrication and protection from drying and physical trauma to the ocular surface itself comes from the transmembrane mucin expressed on the surface of the entire ocular surface epithelium. It has also been proposed that this transmembrane mucin plays a critical role in spreading and maintaining the tear film structure through its interaction with the secreted gel-forming mucins of the tear film.

Mucins are the most important component in the tear film for promoting lubrication during the blinking process. The rate of shear during blinking can be very high. At such levels damage to cells and subsequent pain will occur if the shearing forces generated during blinking are transmitted to the epithelial surfaces. Two rheological conditions can mitigate the action of the shearing forces due to blinking. Firstly, shear thinning (non Newtonian behavior) of the tear film as the shear forces increase will result in a reduction of the apparent viscosity. Secondly, the energy

associated with the shear forces can be partially absorbed by the elastic component of the tear film. These rheological conditions are provided by the viscoelastic properties of ocular mucin secretions, both in the gradient concentration of the fluid layer and in the gel near the epithelial surface. As a result, during eye movement the mucin can act on the stress gradient across the tear film and reduce the shear forces to near zero at the cell surfaces. Current commercial artificial tear products do not achieve the viscoelastic properties of human tears and have very limited retention time and lubricity effect in the eye.

The search for mucin-like polymers has extended into the area of bio polymers, with particular emphasis on the naturally occurring polysaccharides. One polymer, hyaluronic acid, and its sodium salt have received much attention over the past several years. In fact, one commercial product, Hylashield®, based on a high molecular weight sodium hyaluronate, has been successfully marketed as a dry eye treatment solution. The use of hyaluronic acid in artificial tear solution compositions is also taught in U.S. Patents 5,460,834 and 5,106,615, both of which are incorporated by reference in their entirety. Other polysaccharides, such as carrageenan, tamarind gum and keratan sulfate have been claimed to have utility in artificial tear solutions as disclosed in U.S. patents 5,403,841 and 5,460,834 and PCT publications WO97/28787, all of which are incorporated by reference in their entirety. In addition, polysaccharides, such as alginate, dextran, scleroglucan and xanthan have been used, or have been proposed for use in ophthalmic solutions.

Prior art clearly recognizes the importance of mucin in the natural tear fluid as a wetting agent, viscoelastic gel former, lubricant and barrier to bacterial adhesion. Limited success with so many various synthetic and substitute polymers indicate that supplementing the tear fluid with a compatible mucin from an exogenous source would appear to be a more direct and preferred method for addressing dry eye conditions. Part of the problem in the development of ocular surface changes in dry eye disease may be the dehydration of the mucus gel and subsequently the mucin layer of the cellular surface. Supplementing the tear fluid with mucin in an aqueous solution would be expected to help maintain the natural surface mucin layer of the eye

by both the addition of the additional mucin molecules and the hydration provided by the aqueous vehicle.

Perhaps one reason that mucin-based ophthalmic solutions have not been developed is the limited commercial availability of mucin. The mucins that are available are partially purified from bovine submaxillary glands, or from porcine guts. These by-products of the meat packing industry are distributed by Sigma Chemical Company (St.Louis, MO) and Worthington Biochemical Corp. (Freehold, NJ). The most notable problem with currently available commercial mucins is their very poor quality. For example, fractionation of BSM mucin from Sigma by SDS-PAGE reveals that the preparation is heavily contaminated by low molecular weight proteins that are either degraded mucin, or proteins unrelated to mucin.

The patent literature reveals one reference to the use of mucin in sterilized, preserved and stable solutions. U.S. patent 4,438,100, incorporated by reference in its entirety, describes mucin-containing solutions for application to sensitive mucous membranes of the oral cavity, the nasal system and the eye. The mucins utilized in this invention are non human mammalian mucins selected from the group consisting of buccal and gastrointestinal mucins. In fact, the source of their mucins is mucus, a mature and complex secretion containing a mixture of various mucin molecules as well as other proteins and associated contaminants of secretion. The is no distinction made between secreted mucins and mucins expressed by the surface cells of the oral cavity or gastrointestinal mucous membranes. The inventors provide examples of mucin-containing solutions for use as artificial saliva, but do not teach the preparation of ophthalmic solutions. In fact, the inventors discuss the potential use of mucin-containing ophthalmic solutions in conjunction with contact lens care. It is evident that the inventors did not contemplate the use of mucin as a tear supplement.

SUMMARY OF THE INVENTION:

The present invention relates to ophthalmic preparations for use as a tear film supplement. More specifically, the invention relates to an aqueous formulation to be instilled into the eye, or in which to pre soak or store an object to be inserted into the eye, such as a contact lens, an ointment, or a solid device to be inserted into the